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Substrate-controlled product-selectivity in the reaction of Bestmann-Ohira reagent with N-unprotected isatin-derived olefins

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A mild and efficient reaction of Bestmann-Ohira reagent with N-unprotected isatin-derived olefins has been developed for the selective synthesis of spiro-pyrazoline-oxindoles and tricyclic pyrazoles. The reaction features an attractive product-selectivity depending on the substituent on isatin-derived olefin. Treatment of 3-aryl/alkylideneoxindoles with BOR afforded spiropyrazoline-oxindoles, whereas 3-phenacylideneoxindoles furnished pyrazoloquinazolinones via a unique ring expansion reaction.

Introduction

Organophosphorus compounds have drawn much attention due to their extensive applications in agrochemical and pharmaceutical industries. 1 Among various organophosphorus compounds, phosphonylated azaheterocycles in general and phosphonylpyrazoles in particular, are well-known for their remarkable bioactivity profile, and thus have received considerable attention over the years. 2 Consequently, a number of strategies have been developed for the synthesis of this scaffold. The most common methods include the condensation reactions involving hydrazines and cycloaddition reactions of diazocompounds to vinylphosphonates. 3 More recently, an attractive strategy has been developed for the synthesis of phosphonylpyrazoles by employing the Bestmann-Ohira reagent (BOR) as a 1,3-dipolar species in cycloaddition reaction with nitroalkenes. 4 Subsequently, the utility of BOR, a reagent better known for its ability to homologate aldehydes to alkynes under mild conditions, 5 has been well established as a versatile 1,3-dipole for the synthesis of several phosphonylated pyrazoles and pyrazolines (Scheme 1, eq 1). The research groups of Namboothiri and Smitenta independently developed very efficient strategies for the synthesis of densely functionalized pyrazoles from various activated olefins such as dicyanostyrenes, vinylsulfones, chalcones and alkynes. 6,7 Furthermore, the strategy was successfully employed for the diastereoselective synthesis of spiropyrazolines by choosing substituted chalcones as dipolarophiles. 8,9

Recently, we have reported the synthesis of vinyl pyrazoles using BOR and α,β-unsaturated aldehydes, and the reaction proceeds via a domino 1,3-dipolar cycloaddition/homologation reaction sequence. 8 In view of our continued interest in the chemistry of BOR, we envisioned that if the reaction of dimethyl diazomethylphosphonate (DAMP) anion generated in situ from BOR is conducted with N-unprotected ylidenenoindoles, it may undergo a formal 1,3-dipolar reaction to afford spiro-pyrazoline-oxindoles, a privileged scaffold having very interesting physical, structural and biological properties. 9,10 To realize our goal, we first tested the reaction of BOR with arylidene oxindole as the electrophilic component for the anticipated 1,3-dipolar cycloaddition reaction and to our delight, the reaction afforded the spiro-phosphonylpyrazoline-oxindole in good yields and reasonable diastereoselectivity. Surprisingly, in an attempt to expand the scope of the reaction by employing phenacylideneoxindoles as the coupling partner for BOR under identical conditions, we observed an unprecedented rearrangement furnishing pyrazoloquinazolinones (Scheme 1, eq 2). Herein, we report this...
unique observation on substrate-controlled product-selectivity resulting in a simple, efficient, and straightforward approach to the synthesis of densely functionalized spiro-pyrazoline-oxindoles and pyrazoloquinazolinones. Notably, the selectivity depends on the electronic nature of the substituent at the β-position of the isatin-derived olefin and N-protection at the isatin-derived olefin was not needed for the reactivity.

The envisioned reaction was investigated using 3-benzylidenoxindole as a model substrate and delightfully, the reaction of 1a with BOR 2 and K₂CO₃ proceeded smoothly to afford the corresponding spiro-pyrazoline-oxindole 3a in 85% yield. In order to improve the efficiency of the conversion, a brief survey of reaction conditions was conducted using different bases and by varying stoichiometry of the reagents. Though no significant difference in yield was observed on employing different bases for the reaction, we found that 1.5 equiv of BOR and 2.0 equiv of KOH gave the best yield of 95% for the present reaction (eq 3).

With the reaction conditions established, we next turned our attention to evaluate the scope and limitations of our reaction with different type of aryldieneoxindoles. Generally, the reaction displayed excellent functional group tolerance and good diastereoselectivity as shown in Table 1. It was pleasing to find that besides arylidenes, heteroaryl and aliphatic substitutions can also be employed in the reaction. Aryldieneoxindoles with electron-rich and electron-deficient substitutions at 4-position of aryl group provided their corresponding spiro-pyrazoline-oxindoles in good to excellent yields (3b–h). For instance, 4-methoxybenzylidenoxindole underwent the reaction to afford the spirooxindole 3b in 92% yield and the structure of the product was confirmed using X-ray crystallographic analysis. More interestingly, 4-nitro substituted benzylidenoxindole and arylidenoxindole derived from 4-formylphenylboronic acid were compatible under the reaction conditions and the products, worthy of further synthetic transformations, were obtained in modest to excellent isolated yields (3h,i). Additionally, arylidene having electron-rich and electron-poor substitutions at the ortho- and meta-positions such as methoxy- and halo- groups proved effective in this transformation and yielded the corresponding products in excellent yield and good diastereoselectivity (3j–n). Heteroaryl substitutions like thiophenyl and furyl were also found to be suitable for the present cycloaddition reactions and the products were isolated in excellent yields (3p,q). We next investigated the use of aliphatic groups and gratifyingly, the treatment of 3-isobutenyldenedoxindole with BOR under basic reaction condition resulted in the formation of the product 3r in 61% yield.

The success of this strategy for the synthesis of a new class of densely functionalized spiro-pyrazoline-oxindoles prompted us to extend this reaction to other electrophilic olefins derived from isatins. To explore the possibilities toward this end, in a pilot experiment, phenacylideneoxindole 4a was exposed to BOR under identical conditions to the one shown in Table 1. Interestingly, the anticipated formal 1,3-dipolar cycloaddition was followed by an unprecedented rearrangement allowing selective access to a novel class of pyrazoloquinazolinones (eq 4). In this context, it is worthy to note that functionalized pyrazoloquinazolinones have shown a broad spectrum of biological activities including AMPA, Gly/NMDA, KA antagonist, benzodiazepine receptor binding agonist, phosphodiesterase 10 A and vaccinia virus inhibitors. Although many methods for the synthesis of pyrazoloquinazolinones are available in the literature, most of them generally require harsh reaction conditions restricting functional group tolerance and usually involve multistep synthetic sequences. A brief optimization of reaction conditions revealed KOH/MeOH as the most effective reaction condition.

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<th>Substrate Scope for the Synthesis of Spiro-phosphonylpyrazoline oxindoles*</th>
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*General conditions: 1 (0.30 mmol), 2 (0.45 mmol), KOH (0.60 mmol), MeOH (5.0 mL) and 25 °C. Isolated yield after column chromatographic purification; dr was determined by 1H-NMR analysis of crude product and the diastereomers were separated using column chromatography.
Having optimized the reaction conditions, we set out to examine the scope of the reaction by varying the substitution patterns at both isatin as well as phenacylidene portions. The electron-withdrawing or electron-donating substitutions at oxindole moiety had little impact on the efficiency of the reaction. Notably, structurally and biologically relevant phenacylidene-5-fluorooxindole afforded the product 5f in 74% yield and the structure was confirmed by X-ray analysis. Oxindoles bearing various heteroatoms at the 5-position were found to be equally amenable for the transformation and substrates with electron-neutral substituents also worked well (5b-g). In the next stage of scope evaluation, we investigated the reactivity of substrates having substitutions at phenacylidene moiety and as seen in Table 2, substrates bearing electron-rich and electron-withdrawing substituents were competent for this reaction and provided the corresponding pyrazoloquinazolinones in excellent yields (5h-I). A wide range of 5-substituted and 5,7-disubstituted oxindoles smoothly underwent the reaction and provided the corresponding pyrazoloquinazolinones in good to excellent yields (5v-z). Next, we examined the scope of aliphatic acyl moiety in the reaction and pleasingly, the reaction afforded the corresponding pyrazoloquinazolinones in moderate yields (5ab-ad).

To further illustrate the synthetic potential of this strategy, we explored a one-pot cycloaddition/click reaction sequence using N-propargyl-3-phenacylideneoxindole 6 as the substrate. Gratifyingly, the reaction gave the corresponding pyrazoloquinazolinone bearing triazole 7 in 71% yield (eq 5) showing the potential of this strategy in constructing densely functionalized molecules in an organized manner.

A plausible mechanism based on literature precedent for the formation of spiro-pyrazole-oxindole is depicted in Scheme 2. The reaction is believed to proceed via a formal 1,3-dipolar cycloaddition reaction of DAMP anion, generated in situ through methanolysis, with isatylidene and a subsequent 1,3-H-shift would afford the spirooxindole 3. A tentative pathway for the formation of pyrazoloquinazolinone 5 based on the outcome of the reaction is shown here. Initially, the reaction proceeds through the pathway described for spiropyrazole formation and subsequently, a spontaneous air-oxidation would result in a strained spirooxindole II, which may further undergo a methanol-mediated rearrangement to deliver stable pyrazoloquinazolinone 5. Spontaneous air-oxidation is presumably an outcome of the extensive conjugation to the benzoyl moiety present at the pyrazole scaffold.

To gain more insight into the mechanism of proposed transformation of spiropyrazole-oxindole to pyrazoloquinazolinones via oxidative rearrangement, an experiment was performed under nitrogen atmosphere to check the role of oxygen in the process. Interestingly, the reaction of substrate 4l with BOR under nitrogen atmosphere afforded spiro-pyrazoline-
oxindole 8 in 46% yield along with 26% of the final compound 5I (Scheme 3). The formation of spiro-pyrazoline-oxindole 8 from 4I under inert atmosphere clearly indicates that pyrazoloquinazolinones 5 are formed through the oxidative rearrangement of spiropyrazoline oxindoles.

Conclusions

In conclusion, an attractive strategy has been achieved for the selective synthesis of spiro-phosphonylpyrazoline-oxindoles and phosphorylpyrazoloquinazolinones from N-protected isatin-derived olefins employing BOR. The reaction features a substrate-controlled product-selectivity to afford either spiropyrazoline-oxindoles or pyrazoloquinazolinones depending on the electronic nature of the substituent at the isatylidene moiety. Broad functional group tolerance, step economy, short reaction time and high efficiency make this strategy synthetically useful. Further investigation on mechanism and study on similar reactivity are currently in progress in our laboratory.

Experimental Section

General experimental information

Unless otherwise specified, all reactions were carried out under air atmosphere in oven-dried round-bottom flasks. Dimethyl 2-oxopropylphosphonate was purchased from Acros and was used without further purification. The reactions were monitored by TLC under inert atmosphere in oven-dried round-bottom flasks. Dimethyl 2-oxopropylphosphonate was purchased from Acros and was used without further purification. The reactions were monitored by TLC without further purification. The reactions were monitored by TLC. Unless otherwise specified, all reactions were carried out under air atmosphere in oven-dried round-bottom flasks. Dimethyl 2-oxopropylphosphonate was purchased from Acros and was used without further purification. The reactions were monitored by TLC without further purification. The reactions were monitored by TLC. Unless otherwise specified, all reactions were carried out under air atmosphere in oven-dried round-bottom flasks. Dimethyl 2-oxopropylphosphonate was purchased from Acros and was used without further purification. The reactions were monitored by TLC without further purification. The reactions were monitored by TLC.

Notes and references

Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.


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